ARVO 2016 Annual Meeting Abstracts

236 Corneal regeneration - Minisymposium
Monday, May 02, 2016 11:00 AM–12:45 PM
Tahoma 4, TCC  Minisymposium
Program #/Board # Range: 1851–1857
Organizing Section: Cornea

Program Number: 1851
Presentation Time: 11:00 AM–11:15 AM
Divergence between Medical Breakthroughs in Corneal Endothelial Treatment and Applied Clinical Practice
Shigeru Kinoshita. Frontier Medical Science and Technology for Ophthalmology, Kyoto Prefectural Univ of Med, Kyoto, Japan.
Presentation Description: Understanding the biological and immunological characteristics of human corneal endothelial cells (CECs) is an essential key to the establishment of new strategies for treating bullous keratopathy caused by corneal endothelial diseases such as Fuchs Endothelial Corneal Dystrophy. In fact, we have been developing a novel ‘cell-injection therapy’ involving the injection of cultured human CECs into the anterior chamber. Our findings in 18 clinical research cases have shown this approach to be extremely promising. However, in order to apply this novel approach to actual clinical practice, several key safety issues must be addressed and assured from the aspect of regulatory science. It is our great hope that ophthalmology-related translational research, such as that described above, will soon receive official governmental approval based upon the accumulated data of safety and efficacy aspects associated with the procedures.
Commercial Relationships: Shigeru Kinoshita, Senju Pharmaceutical Company (P)
Clinical Trial: https://upload.umin.ac.jp/cgi-open-bin/ctrctr.cgi?function=brows&action=brows&type=summary&recptno=R000014592&language=E, UMIN000012534

Program Number: 1852
Presentation Time: 11:15 AM–11:30 AM
Regeneration of the corneal endothelium from iPSC
Shigeto Shimmura. Keio Univ School of Medicine, Tokyo, Japan.
Presentation Description: The cornea consists of the epithelium, stroma and endothelium, all of which contain unique cells that are vital for the homeostasis of the cornea. Stem cells for generating all 3 layers of the cornea have been reported both in mice and humans, and studies to apply these cells to the clinic are underway. Since Yamanaka et. al. successfully developed induced pluripotent stem (iPSC) cells from somatic cells by forced reprogramming using the transcriptional factors OCT4, SOX2, c-MYC, and KLF4, these pluripotent stem cells have become the focus of intense study. Clinical application of stem cells in the treatment of corneal disease will probably involve both somatic stem cells and iPSC cells depending on the disease. The corneal endothelium is an ideal tissue for iPSC application due to the following reasons:
1) Immuno-priveledged properties of the anterior chamber.
2) Small number of required cells.
3) Transparency of the cornea that will allow observation of the cells following transplantation.
Corneal endothelial-like cells from iPSC is possible using inducing culture medium containing factors such as retinoic acid and GSK-3b inhibitors. Cells with neural crest properties can be observed as CD271/CD49d double-positive cells by flow cytometry. Sphere culture of induced endothelial cells further allows the formation of tight junctions, with enhanced expression of N-cadherin and Na,K-ATPase. Preliminary in vivo data in rabbits show that these cells for a monolayer, and can rescue the cornea from edema due to cell loss. Further refinements are underway prior to clinical trials.
Commercial Relationships: Shigeto Shimmura, Keio University (P)

Program Number: 1853
Presentation Time: 11:30 AM–11:45 AM
Corneal stromal tissue regeneration by stromal-derived stem cells
James L. Funderburgh. Univ of Pittsburgh School of Medicine, Pittsburgh, PA.
Presentation Description: The limbal stroma contains a rare population of mesenchymal stem cells immediately subjacent to the epithelial basement membrane. These cells have been termed ‘niches cells’ because they exhibit direct contact with limbal epithelial stem cells and help maintain the LSC phenotype in vitro. The niche cells, when isolated and expanded in culture, exhibit properties of adult stem cells. Our work has shown these corneal stromal stem cells (CSSC) express genes typical of mesenchymal and embryonic stem cells as well as gene products present in neural crest cells and during ocular development. CSSC can be expanded >10 fold before senescence, providing an abundant resource for regenerative applications. When injected into the stroma of a lumican knockout mouse, human CSSC initiate tissue remodeling bringing matrix organization and transparency to the corneas. When CSSC are layered over a stromal debridement wound, fibrotic scar tissue is not deposited rather the ablated tissue is regenerated with matrix indistinguishable the original. This regenerative ability is accompanied by immune-suppressive properties of the CSSC. In vivo, neutrophil infiltration is suppressed after wounding and human CSSC do not elicit T-cell mediated rejection in mouse corneas. In vitro, CSSC block T-cell activation and proliferation. They also modify macrophage phenotype and expression of TGF betas, important mediators of fibrosis. These results implicate the regenerative properties of CSSC with their effect on the immune response of the host. Our current work focuses on the mechanism by which the CSSC exert these effects.
Commercial Relationships: James L. Funderburgh, None

Program Number: 1854
Presentation Time: 11:45 AM–12:00 PM
Implanting collagen scaffolds into the cornea
May Griffith. Linkopping University, Linkopping, Sweden.
Presentation Description: Corneal blindness is a major cause of blindness worldwide. Transplantation with human donor corneas is the only widespread treatment but according to the World Health Organization (WHO), about 90% of visually impaired people live in developing countries where transplantation is not affordable and there is a severe shortage of donated tissues. We have developed an alternative option of ‘re-growing’ the patient’s own cornea with the help of biosynthetic implants made from recombinant human collagen, and have tested these in 10 patients. We recently reinforced the implants with a synthetic lipid polymer, 2-methacryloyloxyethyl phosphorylcholine (MPC) to stabilize then and also modulate the inflammation. These new hybrid implants have now been tested on high risk patients in the Ukraine, who all had painful, ulcerated cornea surfaces, and for whom conventional donor cornea transplantation carried a high risk of rejection. In these patients, the implants were able to retore corneal surface integrity and alleviate the pain. Newer implants that comprise self-assembling peptide analogs of collagen and implants that incorporate silver nanoparticles with anti-bacterial properties, or that incorporate nanoparticles delivering anti-viral peptides have been developed and will be discussed.
Commercial Relationships: May Griffith, UAB Ferentis (S)
Clinical Trial: NCT02277054

These abstracts are licensed under a Creative Commons Attribution-NonCommercial-No Derivatives 4.0 International License. Go to http://iovs.arvojournals.org/ to access the versions of record.
Program Number: 1855
Presentation Time: 12:00 PM–12:15 PM
**Optimizing RAFTs for treating of limbal stem cell deficiency**
**Presentation Description:** This presentation will discuss a collagen-based tissue equivalent (RAFT) which is being developed for the clinical delivery of stem cells to the cornea.
**Commercial Relationships:** Julie T. Daniels, TAP Biosystems (F)

Program Number: 1856
Presentation Time: 12:15 PM–12:30 PM
**The importance of cell therapy controls for a safe, EU-approved Advanced Therapy Medicinal Product application to limbal stem cell deficiency**
Graziella Pellegrini. University of Modena and Reggio Emilia, Modena, Italy.
**Presentation Description:** Ocular burns or infections may destroy the limbus, causing limbal stem cell deficiency. The following invasion by conjunctiva, vessels and stromal scarring leads to corneal opacity and loss of vision. The only way to avoid this pathological picture, is to restore the limbus. Such restoration has been attained through surgical techniques by grafting limbal fragments or by growing in vitro a small limbal fragment to obtain an epithelium to be transplanted on patient.
The presentation will address the description of biological conditions driving the selection of cell therapy versus surgical approaches to such forms of limbal stem cell deficiency. A comparison of risks and related controls requested by the recent ATMP regulation with good clinical practice applied to tissue transplants, will be considered. Clinical experience, results and follow up of the different approaches will be discussed.
**Commercial Relationships:** Graziella Pellegrini, Spouse - J-TEC Japan Tissue Engineering Co., Ltd. (C), Holostem Terapie Avanzate Srl (P), Spouse - Holostem Terapie Avanzate Srl (S), J-TEC Japan Tissue Engineering Co., Ltd. (C), Holostem Terapie Avanzate Srl (S), Spouse - Holostem Terapie Avanzate Srl (P)

Program Number: 1857
Presentation Time: 12:30 PM–12:45 PM
**Limbal Stem Cell Transplantation: Myth or Science**
Sophie X. Deng. Stein Eye Institute, Los Angeles, CA.
**Presentation Description:** Limbal stem cell deficiency (LSCD) is seen in many ocular disorders and leads to functional blindness when it is severe. Limbal stem cell (LSC) transplantation in the form of keratolimbal graft or cultivated LSCs has been the main treatment option to reconstruct a normal corneal epithelial surface. Successful outcome has been reported in many case series since 1997. However, donor cells were not always detected in the recipients of successful allogeneic transplant. In addition, because the criteria of diagnosing and staging LSCD have not been established, there are no standard measures to compare clinical outcomes among studies. The exact mechanism(s) of how the transplanted LSCs reconstruct the corneal epithelial surface are not well understood. Therefore, standardization of the LSCD diagnosis and staging of the disease severity along with the standardization of the LSC transplantation and cultivation protocol would be necessary to evaluate the outcome of LSC transplantation.
**Commercial Relationships:** Sophie X. Deng, patient application #: PCT/US2013/044375 (P)